B1

6, 1996. This application also claims benefit of foreign priority under 35 U.S.C. § 119 and/or 35 U.S.C. § 365 to Application No. 94 14470 filed in France on December 1, 1994; the entire content of which is hereby incorporated by reference.--

Kindly replace the paragraph beginning at page 5, line 19, with the following:

B2

--The objective of a method according to the invention is to prepare a recombinant viral vector for the transfer of an exogenous DNA sequence to a host cell and its expression therein. "Exogenous DNA sequence" is understood to mean a nucleic acid which comprises coding sequences and regulatory sequences permitting the expression of said coding sequences, and in which the coding sequences are sequences which are not normally present in the genome of a parent virus employed in the present invention or, if they are present, are in a different genomic context. In the context of the invention, the exogenous DNA sequence composed of one or more genes. The regulatory sequences may be of any origin.

Kindly replace the paragraph beginning at page 12, line 7, with the following:

B3

--According to another embodiment, a method according to the invention may also be employed to insert at least two DNA fragments within the viral genome, by intermolecular recombination between (i) a first DNA fragment comprising all or part of said genome of the parent virus, (ii) a second DNA fragment comprising a first portion of said exogenous DNA sequence equipped at its 5' end with said flanking sequence A and

(iii) a third DNA fragment comprising a second portion of said exogenous DNA sequence equipped at its 3' end with said flanking sequence B; said second and third DNA fragments containing a homologous sequence overlapping at their respective 3' and 5' ends. As a guide, these sequences which are homologous between the second and third DNA fragments satisfy the same criteria of homology and of length as the sequences A and B. This specific embodiment is especially advantageous for the cloning of large-sized exogenous sequences.--

Kindly replace the paragraph beginning at page 13, line 38, with the following:

--The present invention also covers the use of an infectious viral particle or of a recombinant viral vector prepared according to a method according to the invention, for the therapeutic or surgical treatment of the human body, and in particular by gene therapy. A method according to the invention is intended more especially for the preventive or curative treatment of diseases such as genetic diseases (hemophilia; thalassemias, emphysema, Gaucher's disease, cystic fibrosis, Duchenne's or Becker's myopathy, etc.), cancers and viral diseases (AIDS, herpes infections or infections caused by cytomegalovirus or by papillomavirus). For the purposes of the present invention, the vectors and viral particles prepared by a method according to the invention may be introduced either *in vitro* into a host cell removed from the patient, or directly *in vivo* into the body to be treated. Preferably, the host cell is a human cell, and preferably a lung, fibroblast, muscle, liver or lymphocytic cell or a cell of the hematopoietic line.--

Page 15, before the first line, please insert the following heading:

--**BRIEF DESCRIPTION OF THE DRAWINGS**--.

Kindly replace the paragraph beginning at page 18, line 14, with the following:

--A cassette for the expression of a gene coding for the gp19 protein of the Ad5 E3 region (nucleotides 28731 to 29217) is assembled in the bacteriophage M13mp18 (Gibco BRL) by cloning two PCR fragments, one corresponding to the RSV (Rous sarcoma virus) 3' LTR (oligonucleotide primers oTG5892-SEQ ID NO: 4 and 5893-SEQ ID NO: 5) and the other to the sequence coding for gp19 (oTG5455-SEQ ID NO: 6 and 5456-SEQ ID NO: 7). The vector M13TG1683 is obtained, from which the expression cassette is excised by an *Xba*I digestion. After treatment with Klenow, it is introduced into the *Bsm*I site (blunted by the action of phage T4 DNA polymerase) of pTG8519. The latter is derived from the plasmid puc 19 (Gibco BRL), into which the adenoviral sequences lying between the *Spe*I site and the right-hand end of the genome (nucleotides 27082 to 35935) but lacking the majority of the E3 region (nucleotides 27871 to 30758) have been inserted. pTG1695 is obtained, the *Sca*I-*Spe*I fragment of which, carrying the plasmid sequences, is replaced by a purified equivalent fragment of pTG1659. The latter corresponds to puc 19 comprising the Ad5 sequences extending from nucleotides 21562 to 35826. pTG1697 thereby obtained possesses adenoviral sequences which extend from the *Bam*HI (position 21562) site to the 3' ITR (position 35935), in which sequences the E3 region is replaced by a gp19 expression cassette under the control of the RSV constitutive promoter. The *Dra*I

fragment (position 22444 and 35142 on the Ad5 genome) is purified, and cointroduced into competent BJ-5183 bacteria with pTG3602 linearized with *Spe*I and treated with Klenow. The recombinants carrying a plasmid generated by recombination are screened for the presence of the RSV promoter. pTG3605, a plasmid vector carrying the Ad-gp19+ genome, is thus demonstrated.

Kindly replace the paragraph beginning at page 19, line 9, with the following:

--The infectious power viral genome excised from plasmid pTG3605 is tested according to the protocol already described above. The production of a functional gp19 protein is monitored by co-immunoprecipitation of the antigens of the major histocompatibility complex class I and of the protein (Burgert and Kvist, 1985, Cell, *41*, 987-997).--

Kindly replace the paragraph beginning at page 23, line 32, with the following:

--CAV2 virus (strain Toronto A 26/61; ATCC VR-800) genomic DNA is prepared by the standard technique (amplification on a dog kidney line MDCK GHK, etc., lysis of the cells, purification of the viruses by centrifugation on cesium chloride, treatment with proteinase k and lastly phenol/chloroform extraction). The CAV2 genome, which is 31 kbp in length, is introduced into a plasmid vector by homologous recombination. For this purpose, the left-hand and right-hand ends of the CAV2 genome are isolated by PCR and enzymatic digestion, incorporating a *Not*I site immediately beyond the 5' and 3' ITRs. The

vector pTG4457 is obtained by introducing into p polyII the 5' portion of the viral genome as far as the *Bst*BI site (position 870) followed by the 3' portion starting from the *Sal*I site (position 27800). The complete genome may be reconstituted by cotransformation between the genomic DNA (100 to 500 ng) and pTG4457 digested with *Bst*BI (10 to 100 ng). The viral genome may be excised from the above vector pTG5406 by *Not*I digestion. It is vertified that the DNA is infectious by transfection of 1 to 5 $\mu$g into dog MDCK or GHK cells. The production of plaques is observed.--

In compliance with 37 C.F.R. § 1.823(a), please substitute the attached paper copy of the Sequence Listing between the last page of the specification (page 24) and the first page of the claims (page 31) to replace the Sequence Listing filed with the original application. Please amend the page numbers accordingly.

Please insert the enclosed Abstract, which as required is on a separate sheet, after the last page of the claims (currently page 33).

**IN THE CLAIMS**:

Please cancel claim 1 without prejudice or disclaimer to the subject matter disclosed therein.